



Horizon BCBSNJ
 Medical Necessity Guideline

Section Drugs
Policy Number
Effective Date 6/25/04
Review Date 2/24/06, 7/27/07, 7/25/08

Subject:
BRAND NAME Fuzeon
(Generic) (enfuvirtide)

IMPORTANT NOTE:

*The purpose of this policy is to provide general information applicable to the administration of outpatient prescription drug benefits that Horizon Blue Cross Blue Shield of New Jersey and Horizon Healthcare of New Jersey, Inc. (collectively "Horizon BCBSNJ") insures or administers. **Outpatient prescription drugs are not covered under all Horizon benefit plans.** If the member's contract benefits differ from the pharmacy guideline, the contract prevails. Although a service, supply drug or procedure may be medically necessary, it may be subject to limitations and/or exclusions under a member's benefit plan. If a service, supply drug or procedure is not covered and the member proceeds to obtain the service, supply drug or procedure, the member may be responsible for the cost. Decisions regarding treatment and treatment plans are the responsibility of the physician. This policy is not intended to direct the course of clinical care a physician provides to a member, and it does not replace a physician's or pharmacist's independent professional clinical judgment or duty to exercise special knowledge and skill in the treatment of Horizon BCBSNJ members. Horizon BCBSNJ is not responsible for, does not provide, and does not hold itself out as a provider of medical care. The physician remains responsible for the quality and type of health care services provided to a Horizon BCBSNJ member.*

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FDA-APPROVED INDICATION

Fuzeon in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection in treatment-experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy.

This indication is based on analyses of plasma HIV-1 RNA levels and CD4 cell counts in controlled studies of Fuzeon of 24 weeks duration. Subjects enrolled were treatment-experienced adults; many had advanced disease. There are no studies of Fuzeon in antiretroviral naïve patients. There are no results from controlled trials evaluating the effect of Fuzeon on clinical progression of HIV-1.

Medical Necessity Guideline:

1. The following questionnaire may be used to determine medical necessity of Fuzeon prescriptions.

CRITERIA FOR APPROVAL

- | | | |
|--|-----|----|
| 1. Is the patient ≥ 6 years of age? | Yes | No |
| 2. Does the patient have a diagnosis of human immunodeficiency virus (HIV-1) infection? | Yes | No |
| 3. Will Fuzeon be used in conjunction with the optimized combination antiretroviral regimen? | Yes | No |
| 4. Has the patient received 6 months of Fuzeon therapy?
[Tech Only: If the answer to this question is no, then may skip to question 6.] | Yes | No |
| 5. Is there evidence of HIV-1 replication despite ongoing antiretroviral therapy?
[Skip to question 7.] | Yes | No |

6. Has the viral level decrease or stable virologic response to Fuzeon antiretroviral therapy? Yes
 No
7. Is this request for more than 2 injections per day or 1 kit per month of Fuzeon? Yes No

Guidelines for Approval					
Duration of Approval			6 months		
Set 1		Set 2			
Yes to question(s)	No to question(s)	Yes to question(s)	No to question(s)		
1	4	1	7		
2	7	2			
3		3			
5		4			
		6			

Drug Dispensing Limit Criteria

Drug and Strength	Retail
Fuzeon™(enfuvirtide)	1 kit every 25 days or 3 kits every 75 days
<ul style="list-style-type: none"> • Fuzeon is available in a convenience kit containing 60-single use vials (2 cartons of 30 each) of Fuzeon (90mg strength), 60 vials (2 cartons of 30 each) of Sterile Water for Injection (1.1ml per vial), 60 reconstitution syringes (3cc), 60 administration syringes (1cc), alcohol wipes, package insert, patient package insert, and injection instruction guide. • The duration of 25 days and 75 days is used for a 30 day and 90 day fill period, respectively, to allow time for refill processing. 	

Horizon BCBSNJ Pharmacy Guideline Development Process: This Horizon BCBSNJ Pharmacy Guideline (the "Pharmacy Guideline") has been developed by Horizon BCBSNJ's Pharmacy Drug Policy Subcommittee, Clinical Issues Subcommittee, and Quality Improvement Committee which include practicing physicians and pharmacists. This guideline is consistent with generally accepted standards of medical and pharmacy practice, and reflects Horizon BCBSNJ's view of the subject health care services, supplies drugs or procedures, and in what circumstances they are deemed to be medically necessary or experimental/ investigational in nature. This Pharmacy Guideline also considers whether and to what degree the subject health care services, supplies or procedures are clinically appropriate, in terms of type, frequency, extent, site and duration and if they are considered effective for the illnesses, injuries or diseases discussed. Where relevant, this Pharmacy Guideline considers whether the subject prescription drugs are being requested primarily for the convenience of the covered person or the health care provider. It may also consider whether the prescription drugs are more costly than alternative prescription drugs that are at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the relevant illness, injury or disease. In reaching its conclusion regarding what it considers to be the generally accepted standards of medical and pharmacy practice, Horizon BCBSNJ reviews and considers the following: all credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, physician and health care provider specialty society recommendations, the views of physicians and health care providers practicing in relevant clinical areas (including, but not limited to, the prevailing opinion within the appropriate specialty), the findings and directives of the Food and Drug Administration and any other relevant factor as determined by applicable State and Federal laws and regulations.

BLACK BOX WARNINGS

None

RATIONALE

These criteria meet the Medicare Part D definition of a medically accepted indication. This definition includes uses which are approved by the FDA or supported by a citation included, or approved for inclusion, in one of the Medicare approved compendia.

The intent of the criteria is to ensure that patients follow selection elements noted in labeling, accepted practice guidelines and clinical trials. The patient must have a diagnosis of HIV and the patient should also be experiencing HIV-1 replication despite ongoing antiretroviral therapy. The patient should be currently treated with an optimal antiretroviral regimen.

Fuzeon must be taken as part of the optimal combination antiretroviral regimen. Use of Fuzeon alone may lead to rapid development of virus resistant to Fuzeon.¹⁻⁸

The goal of treatment with prior drug exposure and drug resistance is to re-establish maximal virologic suppression. Viral load and CD4 count are critical for evaluating response to therapy.³ In the clinical trials, the primary objective was to demonstrate that Fuzeon plus an optimal background antiretroviral regimen provided an additional drop in plasma viral load of at least 0.5 log₁₀ copies/mL in 24 weeks. Secondary endpoints included an increase in CD4 count during this same time period.² In patients on a stable antiretroviral regimen, the viral load and CD4 count testing should be repeated every 3-4 months or if clinically indicated. Virologic failure on treatment can be defined after 24 weeks and after 48 weeks.³

Fuzeon is recommended as an alternative agent for HIV prophylaxis after occupational exposure only with expert consultation. Use should be in conjunction with other antiretroviral agents for health-care workers and other individuals exposed occupationally via percutaneous injury or mucous membrane or nonintact skin contact with blood, tissues, or other body fluids associated with a risk for transmission of the virus. Because its mechanism of action occurs before integration of HIV into the host cell, Fuzeon has theoretical benefits for postexposure prophylaxis. However, it requires twice daily subcutaneous injection and is not recommended for routine postexposure prophylaxis. Also, antibodies against the drug may cross-react with viral gp41 to cause false-positive enzyme immunoassay HIV-antibody test results in a patient who is not infected. In such a case, a Western blot test should be negative.^{5,7,8}

The safety and efficacy of Fuzeon has not been established in patients less than 6 years of age or in treatment-naïve patients of any age.^{1,4,6-8} Fuzeon has no activity against HIV-2.¹

Horizon BCBSNJ has requested inclusion of a dosage limit question

ADDITIONAL INFORMATION

Enfuvirtide interferes with the entry of HIV-1 into CD4 cells by inhibiting fusion of viral and cellular membranes. Enfuvirtide binds to the first heptad-repeat (HR1) in the gp41 subunit of the viral envelope glycoprotein and prevents the conformational changes required for the fusion of viral and cellular membranes.

Drug Resistance

HIV-1 isolates with reduced susceptibility to enfuvirtide have been selected in vitro. In clinical trials, HIV-1 isolates with reduced susceptibility to enfuvirtide have been recovered from subjects treated with Fuzeon in combination with other antiretroviral agents.

Cross Resistance

HIV-1 clinical isolates resistant to nucleoside analogue reverse transcriptase inhibitors (NRTI), non-nucleoside analogue reverse transcriptase inhibitors (NNRTI), and protease inhibitors (PI) were susceptible to enfuvirtide in cell culture.

Dosage and Administration:

Adults

The recommended dose of Fuzeon is 90 mg (1 mL) twice daily injected subcutaneously into the upper arm, anterior thigh or abdomen. Each injection should be given at a site different from the preceding injection site, and only where there is no current injection site reaction from an earlier dose. Fuzeon should not be injected into moles, scar tissue, bruises, or the navel.

Pediatric Patients

No data are available to establish a dose recommendation of Fuzeon in pediatric patients below the age of 6 years. In pediatric patients 6 years through 16 years of age, the recommended dosage of Fuzeon is 2mg/kg twice daily up to a maximum dose of 90 mg twice daily injected subcutaneously into the upper arm, anterior thigh or abdomen. Each injection should be given at a site different from the preceding injection site and only where there is no current injection site reaction from an earlier dose. Fuzeon should not be injected into moles, scar tissue, bruises, or the navel. Weight should be monitored periodically and the Fuzeon dose adjusted accordingly.

Pediatric Dosing Guidelines:

Weight		Dose per bid injection (mg/dose)	Injection Volume (90 mg/mL)
Kilograms (kg)	Pounds (lbs)		
11.0 to 15.5	24 to 34	27	0.3 mL
15.6 to 20.0	>34 to 44	36	0.4 mL

20.1 to 24.5	>44 to 54	45	0.5 mL
14.6 to 29.0	>54 to 64	54	0.6 mL
29.1 to 33.5	>64 to 74	63	0.7 mL
33.6 to 38.0	>74 to 84	72	0.8 mL
38.1 to 42.5	>84 to 94	81	0.9 mL
>42.6	>94	90	1.0 mL

CONTRAINDICATIONS/WARNINGS/PRECAUTIONS

Warnings:

Local Injection Site Reactions

The most common adverse events associated with Fuzeon use are local injection site reactions. Manifestations may include pain and discomfort, induration, erythema, nodules and cysts, pruritus, and ecchymosis. Reactions are often present at more than one injection site. Patients must be familiar with the Fuzeon injection instructions in order to know how to inject Fuzeon appropriately and how to monitor carefully for signs or symptoms of cellulites or local infection.

Pneumonia

An increased rate of bacterial pneumonia was observed in subjects treated with Fuzeon in the Phase 3 clinical trials. Because of this finding, patients with HIV infection should be carefully monitored for signs and symptoms of pneumonia, especially if they have underlying conditions which may predispose them to pneumonia, Risk factors for pneumonia include low initial CD4 cell count, high initial viral load, intravenous drug use, smoking, and a prior history of lung disease.

Hypersensitivity Reactions

Hypersensitivity reactions have been associated with Fuzeon therapy and may recur on re-challenge. Hypersensitivity reactions have included individually and in combination: rash, fever, nausea, and vomiting, chills, rigors, hypotension, and elevated serum liver transaminases. Other adverse events that may be immune mediated and have been reported in subjects receiving Fuzeon include, primary immune complex reaction, respiratory distress, glomerulonephritis, and Guillain-Barre syndrome. Patients developing signs and symptoms suggestive of a systemic hypersensitivity reaction should discontinue Fuzeon and should seek medical evaluation immediately. Therapy with Fuzeon should not be restarted following systemic signs and symptoms consistent with a hypersensitivity reaction. Risk factors that may predict the occurrence of severity of hypersensitivity to Fuzeon have not been identified.

Precautions:

Non-HIV Infected Individuals

There is a theoretical risk that Fuzeon use may lead to the production of anti-enfuvirtide antibodies that cross-react with HIV gp41. This could result in a false positive HIV test with an ELISA assay; confirmation western blot test would be expected to be negative. Fuzeon has not been studied in non-HIV infected individuals.

Fuzeon is not a cure for HIV-1 infection and patients may continue to contract illnesses associated with HIV-1 infection. The long-term effects of Fuzeon are unknown at this time. Fuzeon therapy has not been shown to reduce the risk of transmitting HIV-1 to others through sexual contact or blood contamination.

Fuzeon must be taken as part of a combination antiretroviral regimen. Use of Fuzeon alone may lead to rapid development of virus resistant to Fuzeon and possibly other agents of the same class.

Antiretroviral Pregnancy Registry

To monitor maternal-fetal outcomes of pregnant women exposed to Fuzeon and other antiretroviral drugs, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

Nursing mothers

The Centers for Disease Control and Prevention recommends that HIV-infected mothers not breast-feed their infants to avoid the risk of postnatal transmission of HIV. It is not known whether enfuvirtide is excreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, **mothers should be instructed not to breast-feed if they are receiving Fuzeon.**

Pediatric use

The safety and pharmacokinetics of Fuzeon have not been established in pediatric subjects below 6 years of age. Limited efficacy data is available in pediatric subjects 6 years of age and older.

REFERENCES

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2. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. <http://AIDSinfo.nih.gov>. October 29, 2004.
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7. Panel on Antiretroviral Guidelines for Adult and Adolescents. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. Department of Health and Human Services. October 10, 2006; 1-113. Available at <http://AIDSinfo.nih.gov/ContentFiles/AdultandAdolescentsGL.pdf>. Accessed April 2, 2007.
8. Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the use of antiretroviral agents in pediatric HIV infection. October 26, 2006; 1-126. Available at <http://AIDSinfo.nih.gov/ContentFiles/PediatricGuidelines.pdf>. Accessed April 2, 2007.
9. Centers for Disease Control and Prevention. Updated U.S. Public Health Service guidelines for the management of occupational exposures to HIV and recommendations for Postexposure Prophylaxis. MMWR 2005;54(No. RR-9):1-17.

Pharmacy Guidelines can be highly technical and are designed for use by the Horizon BCBSNJ professional staff in making coverage determinations. Members referring to this policy should discuss it with their treating physician or pharmacist, and should refer to their specific benefit plan for the terms, conditions, limitations and exclusions of their coverage.

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